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10/577,343	03/05/2007	Yasuharu Nishimura	P29875	4864

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/577,343	NISHIMURA ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7 and 8* is/are pending in the application.

4a) Of the above claim(s) *1 and 2* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-5, 7 and 8 are all the pending claims in this application.

2. Claim 6 was cancelled and new claim 8 was added in the Response of 1/6/09.

Newly submitted claim 8 is directed to an invention that is similar to the invention originally claimed for the following reasons: the claim is drawn to a diagnostic method for malignant melanoma comprising a kit comprising an antibody against GPC3 or a probe or primer for detecting GPC3 expression.

3. Claims 1 and 2 are withdrawn.

4. Claims 3-5, 7 and 8 are all the pending claims under examination.

5. This Office Action is FINAL.

Information Disclosure Statement

6. The IDS of 1/6/09 has been considered and entered. Applicants have not provided a copy of the English language abstract for EP0561183, therefore, the reference has been stricken on the attached 1449 form. An initialed and signed copy of the 1449 form is attached.

Examiner's Note

7. A revised copy of the PTO 892 form from the Office Action of 6/17/08 is attached wherein the Examiner has corrected the publication date for reference V.

Withdrawal of Rejections

Claim Rejections - 35 USC § 101

8. The rejection of Claim 6 under 35 U.S.C. 101 because the claim did not recite any steps involved in the process is moot for the cancelled claim.

Claim Rejections - 35 USC § 102

9. The rejection of Claims 3-7 under 35 U.S.C. 102(a) as being anticipated by Nakatsura et al. (Clin. Can. Res. 10:6612-6621 (10/1/2004); cited in the PTO 892 form of PTO 892 form of 6/17/08) is withdrawn.

Applicants have overcome Nakatsura by perfecting their priority to 10/29/03 by filing a certified translation of JP 2003-368725 showing support for the rejected claims pursuant to 37 CFR 1.55 and MPEP 201.13.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. The rejection of Claims 3-5, 7 and (new Claim 8) under 35 U.S.C. 103(a) as being unpatentable over Katagiri et al. (20030165954; published 9/4/03; filed January 9, 2003) in view of Desai et al. (J. Med. Genet. 35:476-481 (1998)) *as evidenced by* Nakatsura et al. (Clin. Can. Res. 10:6612-6621 (10/1/2004); cited in the PTO 892 form of PTO 892 form of 6/17/08) is maintained.

New Claim 8 is drawn to a diagnostic method for malignant melanoma comprising a kit comprising an antibody against GPC3 or a probe or primer for detecting GPC3 expression.

For purposes of review, the rejection was set forth in the Office Action of 10/17/08 as follows:

"The diagnostic method was prima facie obvious at the time of the invention over Katagiri in view Desai as evidenced by Nakatsura.

Katagiri discloses detecting the level of expression of one or more drug sensitivity genes such as GPC3 comprises detecting the level of mRNA expressed from the drug sensitivity genes, detecting the level of mRNA expressed from the drug sensitivity genes comprises exposing the mRNA to a nucleic acid probe complementary to the mRNA or performing an INVADER assay, or detecting the level of polypeptide expressed from the drug sensitivity genes comprises exposing the polypeptide to an antibody specific to the polypeptide and detecting the binding of the antibody to the polypeptide [0005]. Katgiri teaches methods for detection of expression of cancer markers (e.g., to determine drug sensitivity scores or drug sensitivity profiles) where expression is measured directly (e.g., at the RNA or protein level), in tissue samples (e.g., biopsy tissue), or in bodily fluids (e.g., including but not limited to, plasma, serum, whole blood, mucus, and urine) [0096]. Katagiri teaches gene expression of cancer markers is detected by measuring the expression of the corresponding protein or polypeptide, for example, GPC3, by any suitable method including immunohistochemistry methods or binding to an antibody raised against the protein (e.g., radioimmunoassay, ELISA (enzyme-linked immunosorbant assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (e.g., using colloidal gold, enzyme or radioisotope labels, for example), Western blots, precipitation reactions, agglutination assays (e.g., gel

agglutination assays, hemagglutination assays, etc.), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc.) [0104-0105]. Katagiri teaches the antibody/antigen can be detected with matrixes, complexes can be dissociated from the matrix, and the level of cancer markers binding or activity determined using standard techniques. Other techniques for immobilizing either cancer markers protein or a target molecule on matrices include using conjugation of biotin and streptavidin. [0162] Katagiri teaches and appreciates GPC3 is a drug sensitive gene and diagnosing GPC3-expressing cancers with diagnostic and quantitative methods but does not specifically disclose that GPC3 expression is associated with skin cancers such as melanoma whereas Desai as evidenced by Nakatsura does.

Desai teaches that a subset of a juvenile polyposis (JP) patient population was found to have dermatological abnormalities including telangiectases and large numbers of pigmented naevi. Increased number of pigmented naevi common followed by including telangiectasia of the skin and mucous membranes, cutaneous and subcutaneous swellings, and skin pits. One patient had a basal cell carcinoma (p. 477, Col. 2, ¶5). Desai teaches that one patient, patient 18, had features consistent with Simpson-Golabi-Behmel (SGB) syndrome, and although "juvenile polyps are not documented as a regular feature of this condition, it is well known to show very variable penetrance, and since macrocephaly and hypertelorism are common features in our cases, it does beg the question as to whether the male excess of cases of JP in our series could be the result of X linked conditions. Mutations in the glypican gene, GPC3, have been found to underly SGB syndrome and should allow us to test for germline mutations in this cohort" (p. 479, Col. 2, ¶1).

As evidenced by Nakatsura, GPC3 gene expression is shown to be inherent characteristic in a skin abnormality such as melanoma. Nakatsura is effective as art to show inherency for the melanoma expression of GPC3 pursuant to MPEP 2131.01:

> ""III. To show that a characteristic not disclosed in the reference is inherent"…Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO, Inc.* 190 F3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999)…Also note that the critical date of extrinsic evidence showing a universal fact *need not antedate* the filing date (MPEP 2124)."

Under the recent KSR decision, the cited references of art are not required to "*explicitly* teach or suggest" all of the steps or elements of a method. The Supreme Court has determined in *KSR International Co. v. Teleflex, Inc.*, 550 U.S._, 82, USPQ2d 1385 (2007), that "a person of ordinary skill attempting to solve a problem will" not " be led only to those elements of prior art designed to solve the same problem……" (KSR, 550 U.S. at_, 82 USPQ2d at 1397). In addition, the court found that "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variant, 35 USC 103 likely bars its patentability" (KSR, 550 U.S. at_, 82 USPQ2d at 1396). Further the court found that the Federal Circuit has erred in applying the teaching-suggestion-motivation test in an overly rigid and formalistic way, in particular by concluding "that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'" (KSR, 550 U.S. at_, 82 USPQ2d at 1397) and has further determined that "…….[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" (KSR, 550 U.S. at_, 82 USPQ2d at 1395). The court further found that "…… the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious" (KSR, 550 U.S. at_, 82 USPQ2d at 1395-1396). Thus, when considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions" ((KSR, 550 U.S. at_, 82 USPQ2d at 1396).

The ordinary artisan would have been motivated and been assured of reasonable success in having produced the diagnostic method at the time of the invention based on Katagiri in view of Desai as evidenced by Nakatsura. Katagiri and Desai teach expression of GCP3 in hyperproliferative disorders and cancer. Katagiri teaches that detecting and quantitating GCP3 is beneficial in the diagnosis of cancers because the gene is a drug-responsive gene and Katagiri teaches different methods for detecting and quantitating gene or protein expression and using antibodies to detect and quantitate the expressed protein. Desai provides motivation to consider GCP3 expression as being correlative for disorders falling within juvenile polyposis which present with dermatological abnormalities including skin cancers and increased numbers of pigmented nevei, and where as evidenced by Nakatsura, GCP3 is inherently expressed by the skin cancer, melanoma. Because Desai expressly teaches that GCP3 may be related to a class of skin-related disorders and Katagiri teaches diagnostic methods and diagnostic criteria for detecting GCP3, and GCP3 expression is inherent to melanomas as evidenced by Nakatsura, the ordinary artisan would have been motivated to identify a tumor marker for skin-related cancers especially melanoma and more especially for a gene like GCP3 which as taught by Katagiri was not only a tumor marker but an important drug responsive element in the treatment. The ordinary artisan would have been reasonably assured of success in having produced the method based on the combined disclosure because Katagiri taught the reagents and method assays to perform such

diagnostic steps for detecting GCP3 gene and protein expression, where Desai provided correlative relation between skin-related cancers or disorders and GCP3 expression levels, and finally that GPDC3 expression is inherent to the melanoma skin cancer as evidenced by Nakatsura. For all of the foregoing reasons, the claimed method was prima facie obvious at the time of the invention over Katagiri in view Desai as evidenced by Nakatsura.

Applicants' allegations on pp. 5-7 of the Response of 1/6/09 in addition to the certified translation of the priority document have been consider and are not found persuasive. Applicants allege "First, KATAGIRI is silent with respect to the use of GPC3 expression detection for malignant melanoma. Indeed, KATAGIRI makes no mention of the detection or diagnosis of skin cancers or melanoma at all. Second, DESAI discloses phenotypic features in juvenile polyposis (JP). DESAI, like KATAGIRI, is silent with regard to the use of GPC3 expression detection for malignant melanoma." Finally, Applicants allege Nakatsura is not effective art in having perfected their priority to 10/29/03 by filing the certified translation of JP 2003-368725.

Response to Arguments

Katagiri recognized GPC3 expression correlated with many cancers and the means for diagnosing those cancers using GPC3 as a tumor marker. Katagiri also disclosed kits for detecting cancers comprising an antibody for GPC3 protein and probes for detecting mRNA for GPC3. The Examiner has identified a reference (Desai) showing a strong correlation between GPC3 and skin-hyper pigmentation disorders which involve hyperproliferation, e.g., a subset of juvenile polyposis patients having the GPC3-associated disorder Simpson-Golabi-Behmel (SGB) syndrome. Even though Desai teaches analyzing the GPC3 gene germline of patients for mutations, it is noted that the instant claims do not distinguish an expressed protein from an expressed mRNA much less the mutated gene itself. The reagents in the method, e.g., an

antibody, a probe or a primer can all be generated against the gene or a gene fragment for GPC3. Therefore, Desai's teaching to identify gene mutations would be overlapping for the method for detecting and measuring GPC3 using the unidentified antibody, the unidentified probe or the unidentified primer as instantly claimed.

As stated in the previous Office Action, MPEP 2124 and 2131.01 state the critical date of extrinsic evidence such as references cited to show a universal fact need not be available as prior art before applicant's filing date or to antedate the filing date." Nakatsura is cited to show that missing descriptive matter in the Desai reference is "necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art (MPEP 2131.01 (III)." Thus Applicants allegation that Nakatsura is rendered moot by their Japanese foreign priority application filing dates is irrelevant.

The rejection is maintained.

Conclusion

11. No claims are allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Examiner, Art Unit 1643
Temporary Full Signatory Authority